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Randomized trial comparing dopamine and dobutamine in preterm infants

A. Greenough, E. F. Emery

Department of Child Health, King's College Hospital, London SE5 9RS, United Kingdom

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Abstract. The aim of this study was to compare the efficacy of two inotropic infusions in treating low BP in preterm neonates. Forty infants with median gestational age 27 weeks (range 23–33) were studied. At trial entry the infants, who all had a systolic BP <40 mmHg despite receiving a colloid infusion, were randomized to receive either a dopamine or dobutamine infusion. The infusions were commenced at a rate of 5 μg/kg per min and, if necessary, this was increased over the 3 h study period to 15 μg/kg per min. There was no significant difference in the gestational or postnatal age or baseline BP of the 20 infants who received dopamine and those 20 who received dobutamine. Three hours after commencing the infusions, although there was no difference in the rate of inotrope infusion between the two groups, the infants who received dopamine had a significantly higher systolic BP, a median of 39 mmHg (range 30–58) compared to a median of 34 mmHg (range 21–46) in the dobutamine group, $P < 0.05$. In addition, 10 infants who received dopamine, but only 3 who received dobutamine, had a systolic BP >40 mmHg ($P < 0.05$). We conclude that dopamine rather than dobutamine infusion is more efficacious in improving the BP of preterm neonates.

Key words: Blood pressure – Dobutamine – Dopamine – Inotrope – Prematurity

Introduction

Inotropic agents are frequently administered to treat critically ill, hypotensive infants, particularly those in whom colloid infusions have been unsuccessful or are contraindicated because of pre-existing fluid overload. The most commonly used inotropes in neonates are dopamine and dobutamine. Dopamine has dopaminergic, β- and α-adrenergic effects. At low doses the dopaminergic effects predominate, resulting in reduced renal and mesenteric vascular resistance. The β-adrenergic effect becomes prominent at intermediate doses, increasing cardiac output, and at relatively high dosages the α-adrenergic effect produces peripheral vasoconstriction [2]. In neonates, however, very low infusion rates can increase BP [8, 15]. Dobutamine has predominantly β-adrenergic effects and some α-adrenergic effects [2]. In paediatric populations [4, 10, 17] it also can influence BP when used in low dosage. Dobutamine, however, has advantages over dopamine, namely it has a smaller peripheral vasoconstrictor effect and is less arrhythmogenic [2]. Thus, it was important to assess if dopamine and dobutamine were equally efficacious in improving BP in preterm infants. We now report the results of a randomized trial in which we have made such a comparison.

Correspondence to: A. Greenough

Patients

Forty infants, 20 in each group, were recruited into the study. All of the patients were ventilated at the time of study. There was no significant difference between the patient characteristics nor the ventilatory requirements of the two groups (Table 1).

This study was approved by the King's College Hospital Ethics Committee.

Methods

Preterm infants with a low BP who had an undamped arterial line (see below) in situ were eligible for entry into the study. Low BP was defined as a BP <40 mmHg [14]. The infants were initially treated by a colloid infusion (5 ml/kg/h – total infusion 15 ml/kg). Consecutive infants whose BP remained low 1 h after such treatment were recruited into the study. The infants were then randomized, by means of opening a sealed envelope, to receive either dobutamine or dopamine. The infusions were initially started at 5 μg/kg per min. If the infant's systolic BP remained <40 mmHg after 1 h at such an infusion rate, this was increased to 10 μg/kg per min. If at 2 h the clinician felt there had been an unsatisfactory BP response then the rate could be in-

Table 1. Patient characteristics and ventilatory requirements

Median (range)	Dobutamine	Dopamine
Gestational age (weeks)	27 (23–24)	27 (23–33)
Birth weight (g)	860 (552–1650)	886 (678–1980)
Gender (M:F)	10:10	9:11
Postnatal age (days)	1 (1–6)	1 (1–6)
Ventilator rate (bpm)	55 (30–100)	60 (23–100)
Peak inspiratory pressure (cmH_2O)	20 (14–44)	22 (14–41)
Inspired oxygen concentration (%)	55 (30–100)	60 (23–100)

creased to 15 μg/kg per min. During the first 3 h in which the inotrope infusions were administered no change was made in the fluid input and, in particular, no colloid infusions were given.

Systolic BP was recorded on all infants immediately prior to (baseline BP) and 3 h after commencing the infusion. The systolic BP was measured from an indwelling arterial catheter. The arterial lines, which had been sited for clinical purposes, were connected via a Medex Accuflush transducer to a Horizon 2000 monitor. The monitor allows continuous display of the arterial waveform and minute by minute changes in the systolic and diastolic BP. The arterial waveform was considered to be damped if there was an absence of the dicrotic notch on the arterial waveform [20] in association with less than <5 mmHg difference in the systolic and diastolic BP. Only systolic BP measurements from non-damped arterial lines were used in this study. The systolic BP was read at 30-s intervals from the monitor's display and the results were averaged over a 10-min period.

Analysis

To assess the efficacy of dopamine and dobutamine in increasing BP, we compared the change in BP at 1 h, that is when both groups were receiving the same infusion rate. In addition, we contrasted the change in BP and absolute BP level after 3 h. The change in BP from the baseline BP recorded at the end of the 1st hour and first 3 h of the infusion was expressed as a percentage of the baseline BP. Differences between groups were assessed for statistical significance using the Wilcoxon rank sum test. The number of infants in each group whose BP was >40 mmhg at 3 h were compared and differences assessed for statistical significance using Fisher's exact test.

Trial size

From the results of 20 preterm infants who had previously been treated for low BP by an inotrope infusion, we calculated a trial population of 40 infants was necessary to detect with 80% power at the 5% level a difference in the change in BP of 10% in response to the inotrope infusion.

Results

There was no significant difference in the baseline BP of the two groups, but the BP level 3 h after the infusions were commenced was significantly greater in the dopamine group ($P < 0.05$), (Table 2). At the end of the 1st hour of the infusion, when all infants were receiving 5 μg/kg per min of either dopamine or dobutamine, the change in BP tended to be greatest in the dopamine group (median 17%, range −3% to +95%) compared to a median of 11%, range −25% to +50% in the dobutamine group. The change in BP over the 3 h period was significantly higher in the dopamine compared to the dobutamine group ($P < 0.05$) (Table 2). At the end of the 3 h period ten infants in the dopamine group had a systolic BP >40 mmHg, compared to only three in the dobutamine group ($P < 0.05$). There was no significant difference in the infusion rate 3 h after commencing the infusion between the two groups. Only one infant was receiving an infusion rate at 15 μg/kg per min at 3 h, this infant was in the dobutamine group.

Table 2. BP and infusion rates

Median (range)	Dobutamine	Dopamine
Baseline BP (mmHg)	30 (21–34)	30 (20–34)
BP at 3 h (mmHg)	34 (21–46)	39 (30–58)
Change in BP over the 3 h period (%)	11 (−6 to 45)	23 (−3 to 100)
Infusion rate at 3 h (μg/kg/min)	10 (5–15)	5 (5–10)

Discussion

Our results suggest that dopamine rather than dobutamine is the more effective agent in improving the BP of preterm infants. Infants were regarded as having low BP if their systolic BP was <40 mmHg. This level was chosen, as this is our routine clinical practice and also has been previously recommended [14]. The level may be inappropriate for the most immature infants included in the study, but few normative data are available on which to base a more accurate diagnosis of hypotension for such infants. There was no significant difference in the baseline BP of our two groups, thus we feel it unlikely that our use of a single level of BP on which to diagnose low BP biased our results.

We chose to use a definition of low BP involving the systolic rather than the mean BP. Only the systolic BP level can be measured accurately by non-invasive techniques [18] which are the only methods that can be used in infants without arterial lines. Thus, by quoting systolic BP levels, our results are applicable to all neonatal units regardless of which BP measurement technique they use. Other groups [12, 13], however, have chosen to use the mean BP, for if only invasive BP measurements are made, certain systolic readings may be inaccurate due to damping of the arterial waveform. That complication, however, is most likely to occur with advancing postnatal age [7] and, in the present study, the majority of patients were less than 2 days of age. In addition, we recruited only infants whose lines had an undamped arterial waveform as assessed by strict criteria [20]. Thus we feel our use of systolic BP measurements was appropriate and accurate.

During the first 3 h of the trial no change was made in fluid management and, in particular, no further colloid infusions were given. There was no significant difference in the gestational or postnatal age of the two groups, nor in their ventilator requirements suggesting they had a similar severity of respiratory illness. The only significant difference, therefore, between the groups was the type of inotropic agent received. At 3 h the infants who received the dopamine infusion had a significantly higher BP, yet tended to be receiving a lower infusion rate. Our results, therefore, suggest that dopamine was the more efficacious inotrope. In support of that hypothesis is our finding of a greater change, although not significant, in BP in the dopamine group after 1 h of the infusion when all infants were receiving the same infusion rates regardless of whether this was an infusion of dopamine or dobutamine.

The duration of our study was limited to 3 h, as we felt this was the maximum period it was appropriate to study the effect on BP of a single agent and this protocol followed our routine clinical practice. At the end of the 3 h period there were still patients in both groups who had low BP according to our original criteria [14]. The number of patients whose BP remained <40 mmHg at that time, however, was greater in the dobutamine group, again suggesting dopamine had the superior BP elevating effect. We speculate that this effect may be sustained as in a previous study, [8] which investigated the effect of low dose dopamine on renal function, we found the associated BP elevation was present 24 h after commencing the infusion.

Early studies [3, 11, 16] suggested that children compared to adults appeared less sensitive to dopamine and, as a consequence, high infusion rates should be used. In addition, marked interindividual variation in the response to dopamine was noted [6]. This was explained by possible differences in the amount of infused dopamine used for synthesis of noradrenaline stores [9] or protein binding [1]. In a homogeneous population, as included in the present study, however, similar infusion rates in newborn infants gave uniform plasma concentrations [15] and low-dose dopamine in infants and children affected both BP [19] and ventricular performance [15]. Increases of mean systemic arterial BP have been observed at dosages as low as 0.8 μg/kg per min. Those data [15, 19] indicate that infants are particularly sensitive to the effects of dopamine and this may explain the superior performance of that agent compared to dobutamine in the present trial. Our findings confirm those in anaesthesized chronically instrumented puppies [5], that is dopamine compared to dobutamine, had a greater BP elevating effect. On the basis of these results we would suggest that, in preterm infants with low BP, dopamine should be used in preference to dobutamine.

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